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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/919,501	08/28/97	O'GORMAN S	SAL2190

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EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	11

DATE MAILED: 08/26/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/919,501	O'Gorman et al
Examiner	**Group Art Unit**
Wilson, Michael C.	1633

☒ Responsive to communication(s) filed on *Jun 22, 1999* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-10, 12-16, 18-26, and 28-45* is/are pending in the application.

Of the above, claim(s) *3 and 45* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 4-10, 12-16, 18-26, and 28-44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment filed 6-17-99, paper number 9, has been entered.

The declaration of Stephen O'Gorman and Geoffrey Wahl filed 6-17-99, paper number 10, has been received and is discussed below.

The Information Disclosure Statement filed Nov. 27, 1998, paper number 7, has been considered and made of record.

The abstract has been amended. Claims 11, 17 and 27 have been canceled. Claims 3 and 45 remain withdrawn from consideration as being drawn to a non-elected invention in paper number 9. Claims 1-10, 12-16, 18-26 and 28-44 are under consideration in the instant application.

Election/Restriction

1. Applicant's election with traverse of Group I in Paper No. 9 is acknowledged. The traversal is on the ground(s) that Groups I and II include overlapping subject matter. This is not found persuasive because transgenic plants and transgenic animals are materially distinct and separate inventions for reasons set forth in the office action of 12-14-98 on page 3.

The requirement is still deemed proper and is therefore -made FINAL-.

Claim Rejections - 35 USC § 112

2. Claims 1-10, 12-16, 18-26 and 28-44 remain rejected under 35 U.S.C. 112, first paragraph. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record set forth in the office action of 12-14-98 on pages 4-11.

Applicants argue the examiner has misrepresented the invention by including obtaining expression in spleen and heart tissue of mice. However, the specification clearly demonstrates obtaining expression of a marker gene in the brain, spleen and heart tissue at low levels. Applicants argue the expression obtained in spleen and heart tissue is minimal and that the expression in testes is over 100 times greater. Applicants point out the specification states the expression in somatic tissues occurs (i.e. brain, spleen and heart tissue), but not to a "functionally significant extent" (page 13 of arguments). Therefore, the marker gene is expressed in heart and spleen but the levels are not functionally significant. However, the specification does not define what "functionally significant expression" is in such a way that one of skill could determine applicants meaning. The bottom line is that marker genes are expressed in brain, spleen and heart tissue of mice at low levels using the instant invention. The specification does not enable one of skill to determine whether the expression of any gene is functionally significant in the instant invention.

In an attempt to identify enabled embodiments within the specification, the examiner has pointed out that embodiments encompassing ES cells used to make mice expressing marker genes are not enabled because such cells have no disclosed use. Applicants argue the examiner misrepresents the invention because the examples of a mouse expressing a marker gene are meant to illustrate the invention and the claims are not intended to be limited to the scope of the

example. The examiner realizes the cells and mice are intended to provide correlative evidence. However, the production of a ProCre mouse alone is not of use because it does not have a phenotype that distinguishes it from the wild-type mouse. The production of a ProCre/P2Bc mouse alone is not of use because it is not clear the recombined P2Bc is functional in any tissue, because expression of P2Br occurs in the heart, spleen, brain and testes, and because expression of a marker gene is not of apparent use as disclosed in the specification.

The specification does not provide adequate correlation between mice expressing marker genes and mice expressing other proteins such that a transgenic animal with a predictable phenotype could be made which is the purpose of the specification. Applicants argue it is common in the art to use marker genes as a model for expressing other proteins. Applicants point is true however, transgene behavior was unpredictable at the time of filing. Wall et al. of record teach transgene expression often occurs in unintended tissues. Based on the art recognized unpredictability in the art, one of skill would not be able to determine how to direct expression to tissues other than testes at high levels and spleen, brain and heart tissues at low levels. More significantly, it is not clear what phenotype results from expressing the protein.

Applicants argue the lethal allele can occur because germline transmission would be restricted to rare chimeras in which the level of chimerism was low enough to allow survival and high enough to allow transmission and because the lethality can be masked by cross-breeding with a wild-type animal. Applicants arguments are not persuasive because the level of chimerism required to allow survival and transmission of a transgene is not taught in the specification and

because the specification does not teach how to "mask" lethality by cross-breeding with a wild-type animal.

Applicants argue a demonstration of using mouse ES cells is adequate to enable making and using ES cells from other animals. Applicants argument is not persuasive because the state of the art at the time of filing was such that a number of significant limitation regarding the production of non-mouse transgenic animals exist. The specification does not teach how to superovulate female rats which is not required when using mouse ES cells to make transgenic mice (Robl and Heideman of record). The isolation of ES cells in species other than mice was unpredictable in the art at the time of filing. The specification does not teach obtaining ES cells in species other than mice. The applicants do not provide adequate guidance to isolate, grow or use any ES cells other than those from mice without undue experimentation. In addition, it was unpredictable at the time of filing whether the physiological result of transgene expression in livestock could be determined using transgenic mice (Wall of record). Therefore, it is unpredictable how the mice of the instant invention correlate to transgenic non-mice.

3. Claim 33, 40 and 44 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons set forth in the office action of 12-14-98.

Applicants argue the term"essential" in claim 33 is definite because one of skill would know the essential portion of a gene is the portion required to produce a biological function. Applicants argument is not persuasive because some biological functions may be considered

essential to some of skill, but not to others. For example, expression of a cytokine at low levels may have one effect on the immune system but expression at high levels may have another effect. One of skill may consider only high levels of expression essential to an invention. The specification does not define "essential" portions of any gene of interest such that one of skill could determine applicants meaning.

The phrase "recombinase responsive construct" in claim 40 is indefinite because it is not defined in the specification and does not have a meaning in the art.

Claim 44 is unclear because it does not result in a step wherein the recombinant livestock (with a non-wild type phenotype) occurs.

Claim Rejections - 35 USC § 102

4. The rejection of claims 1-2 and 4 under 35 U.S.C. 102(a) as being anticipated by Lewandoski et al. (1997, Current Biology, Vol. 7, pages 148-151) is withdrawn in view of the Declaration by Stephen O'Gorman and Geoffrey Wahl filed 6-17-99, paper number 10, which states applicants were in possession of the invention prior to the publication of Lewandoski et al.

Claim Rejections - 35 USC § 103

5. Claims 1-2, 4-5, 10, 12-16 and 18-19, 24-26 and 28-44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al. (1994, Science, Vol. 265, pages 103-106) in view of Zambrowicz et al. (1994, Biology of Reproduction, Vol. 50, pages 65-72) and Lakso et al. (June 1996, Proc. Natl. Acad. Sci., Vol. 93, pages 5860-5865).

Gu et al. teach producing mouse ES cells comprising a nucleic acid construct comprising a T-cell specific promoter operatively linked to Cre recombinase and excising a selectable marker from ES cells using the Cre-lox system (page 104, column 1, line 18; page 104, Figure 1; page 105, column 2, line 17 through the end of the page). Zambrowicz et al. teach the sperm-specific promoter, MP1 (page 65, column 2, line 15). One of skill would have been motivated to combine the Cre-loxP system and the MP1 promoter to eliminate *in vitro* ES cell manipulation to obtain germ-line transmission of a recombined transgene. Motivation to combine is provided by Lakso et al. who state the need to obviate the extended culture of ES cells in order to expose the ES cells to recombination by directing recombination to the embryo (page 5865, column 1, first full paragraph). A sperm-specific promoter operatively linked to Cre recombinase would produce sperm used to fertilize eggs and obtain recombined embryos, thus obviating the extended culture and genetic manipulation of ES cells as suggested by Lakso et al.

Applicants argue the claims are distinguished over the art because the nucleic acid constructs comprise a germline-specific, tissue specific or inducible promoter operatively associated with a recombinase coding sequence. In particular, applicants point out that claims 28-31 are directed toward excising an active marker gene from ES cells comprising a vector encoding a germ-line specific promoter operatively associated with a recombinase coding sequence and a marker gene flanked by recombinase recombination sites, said marker gene operatively associated with a germ-line specific promoter. Applicants argue Gu et al. and Zambrowicz et al. do not suggest using a germ-line specific promoter and the references differ

from the instant invention. Applicants arguments are not persuasive because the combined teachings of Gu et al., Zambrowicz et al. and Lakso et al. teach all the limitations of the claims, provide motivation to combine the references and provide a reasonable expectation of success in making and using the claimed invention. The system taught by the combined teachings of Gu et al., Zambrowicz et al. and Lakso et al. is a Cre-lox system with a sperm-specific promoter. This system may be used to excise the marker gene from the ES cells as claimed.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, motivation to combine is provided by Lakso et al. who suggest limiting the extended culture of ES cells when exposing ES cells to recombination by directing recombination to the embryo (page 5865, column 1, first full paragraph). The addition of the sperm-specific promoter taught by Zambrowicz et al. to the vector taught by Gu et al. directs recombination to the embryo and limits the time the ES cells are in culture.

Applicants argue the method of Lakso et al. is inefficient. However, the method of Lakso et al. is entitled "Efficient *in vivo* manipulation of mouse genomic sequences at the zygote stage"

and is demonstrated by the deletion of neo gene *in vivo* (page 5861, column 1, "Results"). Furthermore, applicants claims do not require any certain level of efficiency.

6. Claims 1, 6-9 and 20-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gu et al. (1994, Science, Vol. 265, pages 103-106) in view of Zambrowicz et al. (1994, Biology of reproduction, Vol. 50, pages 65-72) and Lakso et al. (June 1996, Proc. Natl. Acad. Sci., Vol. 93, pages 5860-5865) as applied to claims 1-2, 4-5, 10, 12-16 and 18-19, 24-26 and 28-44 above, and further in view of Onouchi et al. (1995, Mol. Gen. Genet., Vol. 247, pages 653-660).

The combined teachings of Gu et al., Zambrowicz et al. and Lakso et al. teach producing ES cells comprising a vector comprising a sperm-specific promoter in the Cre-lox system. This system may be used to excise a marker gene from ES cells. Onouchi et al. disclose the FLP recombinase system and the R gene product of *Zygosaccharomyces* system (page 653, column 2, line 8-13).

Applicants repeat the arguments concerning the insufficiency of Gu et al., Zambrowicz et al. and Lakso et al. Applicants arguments are not persuasive for reasons stated above. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596

(Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, motivation to combine Gu et al., Zambrowicz et al. and Lakso et al. with Onouchi et al. is provided by Onouchi et al. who state the Cre-lox, FLP-FRT and R-RS system are all similar and cause recombination (page 653, column 2, line 9). Thus, one of ordinary skill would have recognized the systems were interchangeable and would have realized a reasonable expectation of success in replacing the Cre-lox system with the FLP-FRT or R-RS system since such genetic manipulations were common at the time of filing.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

This application contains claims 3 and 45 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, can be reached on (703) 308-2801. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER